Ocular manifestations in angiokeratoma corporis diffusum (Fabry)

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Angiokeratoma corporis diffusum (Fabry), originally described as a rare skin anomaly, is now recognized as an inborn error of metaboli m. This anomaly is due to a mutation in the X-chromosome, with serious consequences for the male patient. In female carriers the expressivity of the abnormal gene varies greatly, but is rarely as serious as in males.

Symptoms and course

The diagnosis in males can usually be made on the skin lesions, the numerous dark red macules and papules, appearing in the second decade. Severe pain in the hands and feet, increasing in heat and cold, is the first serious complaint. At a later stage the vascular anomalies in the heart and kidneys become a prominent feature. Renal failure is the usual cause of death, which occurs in the fifth decade of life. In other cases neurological symptoms prevail. In a few cases in males symptoms may be absent. In females symptoms are usually less severe and may even be absent. All cases, regardless of the presence of skin lesions, can be diagnosed by skin biopsy. An abnormal lipid can be demonstrated by special staining techniques in the endothelium and muscular wall of the vessels of all calibre (Ruiter, 1953) (Fig. 1). The storage of the substance in various organs leads to the different signs and symptoms of the disease. The nature of the lipid had long been obscure, but has now been shown by Sweeley and Klionsky (1963) to be a glycolipid. The metabolic disorder was identified as a deficiency in ceramide trihexosidase (Brady, Gal, Bradley, Martensson, Warshaw, and Laster, 1967).

FIG. 1 *Lipid in vascular walls stained with Sudan black*

Ocular symptoms

In patients with angiokeratoma and serious renal involvement, hypertensive retinopathy can occur, as Wallace (1958) described in one of his cases. These findings are not typical of the disease. The ocular symptoms which typically occur in angiokeratoma were first described by Weicksel (1925).

(1) *Vascular lesions in conjunctiva and retina*

Conjunctiva The vessels of the bulbar and palpebral conjunctiva show ampullary and saccular aneurysms of the small venules with stasis and thrombosis in some cases.

Retina The vascular lesions in the retina consist of segmental dilatation and tortuosity of the venules. Tortuosity was also described in the arteries. The vascular lesions in conjunctiva and retina may be regarded as identical to the dilated vessels in the skin.

(2) *Corneal opacities*

These were described by Weicksel (1925), Pompen, Ruiter, and Wyers (1947), and Spaeth and Frost (1965).

The typical lesion is a whirl-like opacity in the superficial layers of the cornea (Fig. 2).

FIG. 2 Slit-lamp photographs of corneal opacities in Case 12

Streaks of a more or less dense opacity extend from near the centre of the cornea to the periphery. The lesion can be easily detected in some cases. In the majority of our patients, however, the corneal changes were slight, the earliest lesion being a diffuse corneal haziness (Patient 5).

The opacity is sometimes described as having a yellowish appearance, but was of a whitish dust-like character in our patients.

A histological study of the condition was carried out by Weingeist and Blodi (1971). They found intraepithelial storage, reduplication of the basement membrane, and amorphous material between basement and Bowman's membranes.

(3) *Opacities in the lens*

These were described in a number of cases by Spaeth and Frost (1965).

(4) *Anomalies of the disc*

Wallace (1958) described an irregular and slightly hazy border to the disc in two cases, both in the same family. In one of these, optic atrophy was also present. Spaeth and Frost (1965) mentioned peripapillary as well as perimacular oedema in one case. The condition seems to be rare, and was only found in one of our patients (Case 21). A slightly choked disc on both sides was seen during the development of severe neurological symptoms, which could be interpreted as disseminated sclerosis, but also could be caused by lipidosis. In this patient there was no hypertensive retinopathy. From this case as well as from the literature, it cannot be stated whether the choked or atropic disc is a typical finding in angiokeratoma.

Description of cases

Eighteen patients will be described. Cases 1 to 13 belonged to Family B (Fig. 3) and Cases 14 to 17 to Family F (Fig. 4).

FIG. 3 *Family B* FIG. 4 *Family F*

Case 1, a man aged 37, proband; B, IV, 3.

OPHTHALMOLOGICAL FINDINGS

Conjunctiva In the right eye, in the temporal bulbar conjunctiva, a very irregular tortuous vessel was present (Fig. 5, overleaf).

FIG. 5 *Tortuous conjunctival vessel in Case 1*

Corneae Both showed a few streaks of the typical superficial opacity.

Fundi In the right eye a segmental dilatation of the superior temporal vein was present (Fig. 6).

FIG. 6 *Segmental dilatation of retinal vein in Case 1*

SKIN

Typical lesions. Severe pain in hands and feet. No renal symptoms.
Biopsy positive for lipid staining.

Case 2, a female aged 34, sister of Case 1; B, IV, 4.

OPHTHALMOLOGICAL FINDINGS

Conjunctiva In the right eye, in the temporal bulbar conjunctiva, an irregularly dilated vessel was present, while some smaller vessels showed saccular distensions.

Corneae In both corneae, in the infero-nasal quadrants, some streak opacities were seen.

Fundi The retinal vessels showed no abnormalities.

SKIN

There were a few skin lesions. The biopsy was positive.

Case 3, a girl aged 8, daughter of Case 1; B, V, 5.

OPHTHALMOLOGICAL FINDINGS

Conjunctival vessels No abnormality was seen.

Corneae There was a very distinct vortex of streak opacities in the superficial layers of both corneae.

Fundi The retinal vessels were normal.

SKIN

There were no clinical symptoms. The biopsy positive for lipid staining.

Case 4, a female aged 56, mother of Cases 1 and 2; B, III, 7.

OPHTHALMOLOGICAL FINDINGS

In the skin of the left upper eyelid some dilated vessels were seen.

Conjunctiva The vessels showed no abnormalities.

Corneae A vortex of opacities was seen especially in the right eye.

Fundi In the left fundus the infero-temporal vein showed segmental dilatation (Fig. 7).

FIG. 7 *Segmental dilatation of the inferior retinal vein in Case 4*

SKIN

There were very few lesions. The biopsy was positive for lipid staining.

Case 5, a boy aged 11, son of Case 4, half-brother of Case 1; B, IV, 10.

OPHTHALMOLOGICAL FINDINGS

The conjunctival vessels of the left eye showed saccular aneurysms.

Corneae There was no vortex to be seen. A slight haziness of the superficial layer of the corneae was seen as if the epithelium was powdered. The condition is, however, difficult to differentiate from a normal appearance.

Fundi The left fundus showed tortuosity of the vessels at the posterior pole (Fig. 8).

FIG. 8 *Tortuosity of retinal vessels in Case 5*

SKIN

There were no skin lesions. The biopsy was positive for lipid staining.

Case 6, a boy aged 9, son of Case 2; B, V, 6.

OPHTHALMOLOGICAL FINDINGS

Corneae In both nasal corneae the vortex of opacities was clearly seen.

Fundi There was no abnormality of the vessels.

SKIN

There were no lesions. The biopsy was positive for lipid staining.

Case 7, a boy aged 6, son of case 2; B, V, 7.

OPHTHALMOLOGICAL FINDINGS

Conjunctiva A distinctly dilated saccular vessel was to be seen temporally in the conjunctiva of the right and left eyes.

Cornea In the right cornea there was a horizontal streak. Only if the typical picture is known, can such a small streak be recognized.

Fundi No distensions were seen in the retinal vessels, but there was a very distinct tortuosity both of the arteries and venules.

As the patient was a small boy, no fundus picture could be taken.

SKIN

There were no lesions. The biopsy was positive for lipid staining.

Case 8, a female aged 34, sister of Case 1; B, IV, 5.

OPHTHALMOLOGICAL FINDINGS

Corneae A distinct vortex was to be seen in both corneae.

Fundi There was an irregularity of the lumen of the right superior temporal vein.

SKIN

There were a few lesions. The biopsy was positive.

Case 9, a boy aged 15; B, V, 10.

OPHTHALMOLOGICAL FINDINGS

Conjunctiva In the right and left eye on the temporal side, conjunctival vessels showed saccular distensions.

Corneae In the right eye the superficial vortex form opacity was clearly to be seen; in the left eye it was only of a very shadowy nature.

Fundi There was distension of the right inferior veins (Fig. 9).

FIG. 9 *Segmental dilatation of right inferior vein in Case 9*

SKIN

There were lesions on the scrotum. The biopsy was positive for lipid staining.

Case 10, a girl aged 12; B, V, 12.

OPHTHALMOLOGICAL FINDINGS

Corneae In the left cornea on the nasal side, some radially arranged streaks were to be seen, as in Case 14. The right cornea showed no abnormality.

SKIN

There were no lesions. The biopsy was positive for lipid staining.

Case 11, a girl aged 6; B, V, 13.

OPHTHALMOLOGICAL FINDINGS

Corneae On the nasal side of both corneae some streaks were to be seen, radially arranged, as if belonging to a vortex, of which only the nasal part was present.

SKIN

There were no lesions. The biopsy was positive for lipid staining.

Case 12, a female aged 39; B, IV, 2.

The patient's father (B, III, 2) died at the age of 45 from renal complications of angiokeratoma.

OPHTHALMOLOGICAL FINDINGS

Corneae Vortex opacity.

SKIN

There were no lesions. The biopsy was positive for lipid staining.

Case 13, a boy aged 17, son of Case 12; B, V, 3.

OPHTHALMOLOGICAL FINDINGS

Corneae The vortex opacity was present in both corneae, consisting of a pattern of very delicate streaks.

Fundi No abnormality was to be seen.

SKIN

There were a very few skin lesions. The biopsy was positive for lipid staining.

Family F

Case 14, a female aged 24; F, II, 1. The father of this patient died at the age of 36 from renal failure.

OPHTHALMOLOGICAL FINDINGS

Corneae There was a typical vortex in both corneae, more pronounced on the right side.

SKIN

There were very few lesions. The biopsy was positive for lipid staining.

Case 15, a female aged 23, sister of Case 14; F, II, 2.

OPHTHALMOLOGICAL FINDINGS

Conjunctiva On both sides there were temporally distended saccular vessels.

Corneae Very distinct vortical opacities in both corneae.

SKIN

There were occasional lesions. The biopsy was positive for lipid staining.

Case 16, a female aged 18, sister of Case 14; F, II, 3.

OPHTHALMOLOGICAL FINDINGS

Corneae There were temporal and nasal whirl streaks in both corneae.

SKIN

There were occasional lesions. The biopsy was positive for lipid staining.

Case 17, a female aged 15, sister of Case 14; F, II, 4.

OPHTHALMOLOGICAL FINDINGS

Corneae There were very distinct vortex opacities in both eyes.

SKIN

There were no lesions. The biopsy was positive for lipid staining.

In patients F, I, 3; II, 6 and 7, diagnosis was made by skin biopsies. No ophthalmological investigation was possible, and general investigation was negative.

Case 18, a man aged 34, not belonging to the two sibships described above.

OPHTHALMOLOGICAL FINDINGS

Conjunctiva The bulbar conjunctiva in both eyes showed small saccular distensions.

Corneae Small streaks of superficial opacity were seen; these were not, however, of the typical vortex pattern.

Fundi The discs, which had been choked on both sides in the course of the disease, were now sharply outlined. The arteries showed thick walls and narrowed lumina. There was a marked tortuosity of the branches of the inferior temporal vein of the right eye and of the superior temporal vein of the left eye.

GENERAL EXAMINATION

The skin showed the typical picture of angiokeratoma: most lesions were localized in the lower lumbar and abdominal region.

SKIN

The biopsy was positive for lipid staining.

In this patient the complaints started at the age of 30, with *neurological* symptoms: chiefly flaccid paresis of both legs. Afterwards he developed transient paralysis of the left oculomotor nerve, and 6 months later, a sudden partial transverse lesion at the 10th thoracic level with severe paresis of both legs. There was a horizontal nystagmus. Sensation for all modalities was disturbed below T.₁₀. This last symptom disappeared in one day, the paresis decreasing gradually. During this time the optic discs were choked on both sides. In the cerebrospinal fluid the cell count was slightly raised. Pandy reaction positive, albumin 65 mg./100 ml., globulin 25 mg./100 ml., glucose 46 mg./100 ml. Colloidal reactions normal.

Although the disturbances of the central nervous system had much in common with those of disseminated sclerosis, they were interpreted as symptoms of the storage disease.

Comment

Our series of patients with angiokeratoma consists of seven male and eleven female patients. In the males skin symptoms were present in four cases, the youngest being 15 years. The three patients without skin symptoms were younger. Skin lesions in female patients were slight in five and absent in six cases.

Ophthalmological findings consisted of abnormalities of the conjunctival vessels (7 patients) or segmental dilatation or tortuosities of the retinal vessels (6 cases). No abnormalities of the lens, as mentioned by Spaeth and Frost (1965) were found in our patients. *Corneal lesions of the typical vortex character were present in all patients.*

The corneal findings have to be differentiated from:

- (a) Chloroquine keratopathy, which can show the same whirlform opacities.
- (b) The hereditary whirlform corneal dystrophy of Fleischer (1910) and Gruber (1946a, b).

Dominant heredity was stressed by Denden (1964), who described two cases, mother and daughter, while thirteen relatives showed no abnormality. Angiokeratoma in these cases cannot be entirely ruled out, because no relatives of the father (grandfather) on the parental side were investigated. Franceschetti (1968) discovered typical Fabry patients in Gruber's cornea verticillata family.

The complete accordance between the corneal findings and skin biopsies in our series is the most important finding. The detection of female carriers at an early age is imperative for eugenic reasons. Slit-lamp examination of the cornea, apart from biopsy, can thus lead to the diagnosis of angiokeratoma.

Summary

A description is given of the ophthalmological and general findings in eighteen patients with angiokeratoma. In all patients skin biopsy was positive. Some showed typical vascular anomalies in conjunctiva and retina. One had severe symptoms of the central nervous system. Typical corneal opacities were present in all cases.

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